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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,665	12/16/2002	Philip O. Livingston	2653/56	9377

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/070,665	LIVINGSTON ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-81* is/are pending in the application.

4a) Of the above claim(s) *1-38 and 60-81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/12/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group III, claims 39-59 in the reply filed on 09/26/05 is acknowledged.

The traversal is on the ground(s) that groups I-II, IV should be recombined, because they share the technical feature of an alpha-(2-8)-polysialic acid-carrier conjugate combined with a saponin, and because Jennings makes no mentions of saponins, and there is nothing in Jennings to suggest that saponins be combined with an alpha-(2-8)-polysialic acid-carrier conjugate.

This is not found persuasive because polysaccharide, including alpha-(2-8)-polysialic acid is a poor immunogen, as taught by Jennings et al, and therefore it would have been obvious to combine the alpha-(2-8)-polysialic acid-carrier conjugate taught by Jennings with an adjuvant, including saponin, a well known adjuvant, to increase the immunogenecity of polysialic acid for making its antibodies.

Thus the technical feature of an alpha-(2-8)-polysialic acid-carrier conjugate combined with a saponin is obvious by Jennings and does not make a contribution to the art, and accordingly, the restriction is proper under PCT Rule 13.1.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, group III, claims 39-59 are examined in the instant application.

It is noted that all the species are combined and examined in the instant application.

CONTINUATION DATA

If applicant desires priority under 35 U.S.C. 1 19(e), 120, 121 and 365(c) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent applications (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. " should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

It is requested that applicant updates the status of all U.S. application numbers in the priority statement. See United States Patent and Trademark Office-OG Notices: 1268 OG 89 (18 -March 2003) "Benefit of Prior-Filed Application".

OBJECTION

1. Claims 39-59 are objected to for the seemingly inadvertent typographic error "or" on the last line of claim 39.

An amendment of claim 39, to replace "or" for example with "of" is suggested to obviate this objection.

2. Claim 48 is objected to for the use of the abbreviated language "CpG, GM-CSF".

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claims 44, 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 44 is indefinite for the use of the language "derivative", in that there is no discrete art recognizing the definition for this term. The term "derivative" encompasses a variety of definitions, i.e. chemical modification, deletions, truncations, substitutions, conjugation, etc.., The metes and bound of the claimed invention cannot be ascertained, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

2. Claim 48 is indefinite for the use of the language "a semi-synthetic saponin-like molecule". It is not clear what is "a semi-synthetic saponin-like molecule", and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 39-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 39-59 are drawn to:

1) A method for treating small cell cancer or neuroblastoma, or metastasis thereof, comprising administering alpha-(2-8)-polysialic acid-carrier conjugate and an adjuvant, wherein the number of sialic acid units in each of the polymers is at least about 10, 14 or 50 or greater, wherein each of the polymers could have an average molecular weight of at least about 10,0000, and wherein the treated subject could have had undergone primary treatment for the cancer (claims 39, 42, 43, 57-59).

2) The method of claim 39, wherein the alpha-(2-8)-polysialic acid polymer could be modified to increase immunogenicity or could be N-propionylated alpha-(2-8)-polysialic acid (claims 40-41).

3) The method of claim 39, wherein the carrier is a keyhole limpet hemocyanin, bovine serum albumin, a promiscuous class II activating polypeptide, or a derivative thereof (claims 44-45), and wherein the ratio of polysialic acid to KLH in the conjugate is from about 25 to about 1000, or about 200 (claims 46-47).

4) The method of claim 39, wherein the adjuvant could be a saponin, QS-21 saponin, GP0100 saponin, a semi-synthetic saponin-like molecule, CpG, GM-CSF, Freud's complete or incomplete adjuvant, or an oil-in-water emulsion (claims 48, 50). The amount of saponin is from about 1 ug to about 2000 ug, the amount of QS-21 is from about 50 ug to about 500 ug, or about 100 ug, and the amount of GPI 01000 is

from about 100 ug to about 2000 ug, or about 500 ug to about 1000 ug (claims 49, 51-54).

5) The method of claim 39, wherein the amount of polysialic acid of the conjugate is from about 1 ug to about 1000 ug or is about 30 ug (claims 55-56).

The specification discloses that the neural cell adhesion molecule modified with long sialic acid polymers is found in neuroblastoma and small cell lung cancer (SCLC)(p.2, last paragraph). The specification discloses that administration of polysialic acid conjugated with KLH produces antibodies in a human patient having SCLC and in mice, wherein said antibodies recognize a SCLC tumor cell line, and could promote complement-mediated tumor cell lysis *in vitro* (p.17-19).

A. One cannot extrapolate the teaching in the specification to the enablement of the claims, because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable. For example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of

common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

Further, the goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. However, Ezzell (J. NIH Res, 1995, 7:46-49) reviews the current thinking in cancer vaccines and states that tumor immunologists are reluctant to place bets on which cancer vaccine approach will prove effective in the long run (see the entire document, particularly last paragraph) and

further states that no one is very optimistic that a single peptide will trigger an immune response strong enough to eradicate tumors or even to prevent the later growth of micrometastases among patients whose tumors have been surgically removed or killed by radiation or chemotherapy (p 48, para 6). In addition, Spitler (Cancer Biotherapy, 1995, 10:1-3) recognizes the lack of predictability of the nature of the art when she states that "Ask practicing oncologists what they think about cancer vaccines and you're likely to get the following response: "cancer vaccines don't work". Ask a venture capitalist or the director of product development at a large pharmaceutical company and you're likely to get the same response." (p 1, para 1).

In addition, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). In addition, Boon teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the method comprising administering alpha-(2-8)-polysialic acid-carrier conjugate and an adjuvant would be effective in treating small cell lung cancer or neuroblastoma.

Moreover, one cannot extrapolate from killing a tumor cell line in vitro to treating a subject having small cell lung cancer or neuroblastoma, because Characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor, due to cell culture artifacts, and one cannot predict whether primary small cell lung cancer cells or primary neuroblastoma or metastastic cells thereof would express an adequate amount of polysialic acids on the cancer cell surface to be an effective target for the antibodies to kill cancer cells White et al, 2001, Ann Rev Med, 52: 125-145, teach that for a successful immunotherapy, besides the specificity of the antigen, other following properties of the antigen should also be considered: The antigen should be present on all or near all of the malignant cells to allow effective targeting and to prevent a subpopulation of antigen-negative cells from proliferating. Further, antibodies have been developed against a broad spectrum of antigens, and whether the antigens shed, modulate or internalize influence the effectiveness of the administered antibody (p.126, second paragraph). Moreover, antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last). Further, changes in expression of antigens on cancer cell surface of cancer cell lines due to cell culture artifacts are common and are well known in the art. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to

prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Tian, J et al, 2004, Physiol Genomics, 17: 170-182, teach culture-induced artifact in macular RPE cells, wherein 950 genes are differentially expressed between native RPE and cultured RPE cells, and wherein 2080 genes are expressed in cultured RPE cells but are not expressed in native RPE cells (abstract, p.176). Similarly, Van Dyke D L et al, 2003, Cancer Genetics and Cytogenetics 241: 137-141, teach that random loss of chromosome 21 (monosomy 21) in patients with hematologic diseases is rare and should be confirmed by in situ hybridization (FISH), and that in most diagnosed cases the random loss of chromosome 21 is more likely due to artifact of culture of cells obtained from the patients (abstract, and p. 140, first column, last two paragraphs before acknowledgments).

The evidence presented thus clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome

constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention.

B. If Applicant could overcome the above 112, first paragraph, claim 44 is still rejected under 112, first paragraph, because it is unpredictable that BSA, when conjugated to a polysialic acid polymer, could increase the immunogenecity of said polymer, such that an antibody specific for polysialic acid could be produced in small cell lung cancer or neuroblastoma patients.

It is noted that polysialic acid, being a polysaccharide, is a poor immunogen (specification, p.3, second paragraph).

Helling, F et al, 1994, Cancer Res 54: 197-203, teach that although BSA is a potent carrier for protein antigens, BSA is not a good carrier for carbohydrate antigens, i.e. BSA when conjugated to ganglioside GD3, or the carbohydrate moiety of GD3 induces high-titer antibodies, but said antibodies are not GD3-specific (p. 201). In view of the above teaching by Helling et al, and since a polysialic acid polymer consists of a polysaccharide, it is unpredictable that BSA when conjugated to a polysialic acid polymer, could increase production of antibodies specific for said polymer. The specification does not disclose that BSA, when conjugated to a polysialic acid polymer, could actually increase the immunogenecity of said polymer. The specification does not teach how to use the claimed conjugate for increasing immunogenecity of polysialic

acid, such that antibodies specific for polysialic acid could be produced in cancer patients.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

October 18, 2005